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(54) Title: CLONING AND CHARACTERIZATION OF 5' FLANKING REGIONS OF A HUMAN AGGREGANASE-1 GENE

(57) Abstract: Disclosed is a nucleic acid comprising Agg promoters and methods of using the same. The invention also provides methods for identifying and treating disease based on the activity of Agg promoters.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/012567

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N15/09 A61P19/02 C12N1/21 C12N5/10 C12Q1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] 18 April 2001 (2001-04-18), "Human DNA sequence from clone RP11-297K8 on chromosome 1" XP002315909 retrieved from EBI Database accession no. AL590714 abstract	1-8, 25, 28, 29
Y		9-14, 16, 17, 26, 27
X	DATABASE EMBL [Online] 3 April 2001 (2001-04-03), MIZUI Y ET AL.: "Homo sapiens ADAM-TS4 gene, promoter region." XP002315910 retrieved from EBI Database accession no. AB039835 abstract	1-8, 16, 17, 25-29
Y	-/--	9-14

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

10 February 2005

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28.09.2006

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/012567

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	<p>-& MIZUI Y ET AL: "Characterization of 5'-flanking region of human aggrecanase-1 (ADAMTS4) gene" MOLECULAR BIOLOGY REPORTS, vol. 27, no. 3, September 2000 (2000-09), pages 167-173, XP002315906 ISSN: 0301-4851 abstract; figures; results and discussion; -----</p>	
X	<p>DATABASE EMBL [Online] 13 December 2001 (2001-12-13), "Human aggrecanase-1 promoter" XP002315911 retrieved from EBI Database accession no. AAI68145</p>	1-8,16, 17,25-29
Y	<p>abstract -& JP 2001 245663 A (EISAI CO LTD) 11 September 2001 (2001-09-11) -----</p>	9-14
X	<p>TORTORELLA M D ET AL: "The role of ADAM-TS4 (aggrecanase-1) and ADAM-TS5 (aggrecanase-2) in a model of cartilage degradation." OSTEOARTHRITIS AND CARTILAGE / OARS, OSTEOARTHRITIS RESEARCH SOCIETY. AUG 2001, vol. 9, no. 6, August 2001 (2001-08), pages 539-552, XP002315907 ISSN: 1063-4584 page 546, paragraph 2 - page 547, paragraph 1 -----</p>	9-14
Y	<p>WO 03/035048 A2 (NOVARTIS AG; NOVARTIS PHARMA GMBH; DAOUTI, SHERIF; KUMAR, CHANDRIKA SA) 1 May 2003 (2003-05-01) page 20, line 7 - page 23, line 20; claims; example 3 -----</p>	9-14,16, 17,26,27
Y	<p>KOSHY P J T ET AL: "The modulation of matrix metalloproteinase and ADAM gene expression in human chondrocytes by interleukin-1 and oncostatin M: a time-course study using real-time quantitative reverse transcription-polymerase chain reaction." ARTHRITIS AND RHEUMATISM. APR 2002, vol. 46, no. 4, April 2002 (2002-04), pages 961-967, XP002315908 ISSN: 0004-3591 abstract; discussion; -----</p>	9-14,16, 17,26,27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/012567

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 15
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-17, 25-29

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17, 25-29

an isolated polynucleotide comprising a nucleic acid sequence selected from the group consisting of SEQ ID Nos. 1-6 or methods using said polynucleotides as well as subject-matter related thereto;

1.1. claims: 1-8, 25, 28, 29 (all partially)

an isolated polynucleotide comprising a nucleic acid sequence of SEQ ID No. 1 or degenerate variants thereof as well as subject-matter related thereto

1.2. claims: 1-8, 25, 28, 29 (all partially)

an isolated polynucleotide comprising a nucleic acid sequence of SEQ ID No. 2 or degenerate variants thereof as well as subject-matter related thereto

1.3. claims: 1-8, 25, 28, 29 (all partially)

an isolated polynucleotide comprising a nucleic acid sequence of SEQ ID No. 3 or degenerate variants thereof as well as subject-matter related thereto

1.4. claims: 1-8, 25, 28, 29 (all partially)

an isolated polynucleotide comprising a nucleic acid sequence of SEQ ID No. 4 or degenerate variants thereof as well as subject-matter related thereto

1.5. claims: 1-8, 25, 28, 29 (all partially)

an isolated polynucleotide comprising a nucleic acid sequence of SEQ ID No. 5 or degenerate variants thereof as well as subject-matter related thereto

1.6. claims: 1-8, 25, 28, 29 (all partially)

an isolated polynucleotide comprising a nucleic acid sequence of SEQ ID No. 6 or degenerate variants thereof as well as subject-matter related thereto

1.7. claims: 9-15

a method of identifying an agent which alters interaction of an Agg-1 promoter gene of claim 7 with a transcription factor binding agent as well as subject-matter related thereto;

1.8. claims: 16, 17

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

a method of identifying an agent which alters expression of Agg using an Agg-1 promoter region as shown in Figure 1 operably linked to a reporter gene as well as subject-matter related thereto;

1.9. claim: 26

a method for screening for test compounds that regulate the activity of an Agg-1 promoter using an Agg-1 promoter disclosed herein operably linked to a reporter gene;

1.10. claim: 27

a method of screening for transcriptional modulators of an Agg-1 promoter using an Agg-1 promoter disclosed herein operably linked to a reporter gene and an inducer or inhibitor of Agg-1 promoter activity;

2. claims: 18-20

a method for assaying a sample for the presence of an Agg-1 nucleic acid as well as subject-matter related thereto;

3. claims: 21-24

a reaction kit for assaying a sample for the presence of metalloproteases as well as subject-matter related thereto;

4. claims: 30-37

a method of treating or delaying onset of disorders associated with articular degradation in an individual comprising administering an Agg-1 promoter gene therapeutic agent as well as subject-matter related thereto;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 15

Present claim 15 relates to a product defined by reference to a desirable characteristic or property, namely to an agent which alters interaction of an Agg-1 promoter gene of claim 4 with a transcription factor binding agent, identifiable according to the method of claim 9. The claim covers all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for no single example of such a product. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/012567

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 2001245663	A	11-09-2001	NONE	
WO 03035048	A2	01-05-2003	EP 1442132 A2 JP 2005507915 T	04-08-2004 24-03-2005

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